California Cancer Commission Studies*
Chapter VIII

Malignant Lymphoma

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THE terms malignant lymphoma or malignant lymphoblastoma are generally used to designate malignant disease of lymphoid tissues. In common usage these are spoken of as lymphosarcoma, leukemia, and Hodgkin's Disease. The nomenclature otherwise is unfortunately highly varied, controversial, and confusing.

Detailed classifications are necessarily those based largely on morphology and are among the trade tools of the pathologist. Such classifications are in a general way of value in estimation of prognosis and radiation sensitivity. Gall and Mallory [1] who have made one of the most exhaustive modern studies of the subject offer a morphologic classification based on a study of some 600 cases. This is readily applicable to clinical use and has sound histologic and clinical correlation. The classification is tabulated below along with the terms of more common usage as a reference for the individual who might encounter some of the less familiar terms:

Malignant Lymphoma (Classification of Gall and Mallory)	Various terms commonly used.
A. Stem cell lymphoma	Lymphosarcoma group; including reticulum cell sarcoma and monocytic reticuloendotheliosis.
B. Clasmatocytic lymphoma	
C. Lymphoblastic lymphoma	Lymphosarcoma, Lymphatic leukemia (acute and chronic)
D. Lymphocytic lymphoma	
E. Follicular lymphoma	Lymphosarcoma, giant follicle type, Brill-Symmers' Disease
F. Hodgkin's lymphoma	Hodgkin's Disease
G. Hodgkin's sarcoma	

The authors of this classification emphasize the fact that leukemia of lymphatic type is of incidental occurrence in malignant lymphomatous disease and that lymph node morphology does not differentiate between lymphosarcoma and lymphatic leukemia. Hematologic leukemic manifestations have been observed in all types of malignancies of lymphoid tissues.

The cause or causes of this group of diseases are unknown. Theories and observations related to their origins are numerous.

GENERAL CLINICAL OBSERVATION

The symptoms which may bring the patient to a doctor are many and varied.

The onset of disease of this type is usually insidious. The process may be present in hematologically diagnosable form before there is objective or subjective evidence that anything may be amiss. This is illustrated infrequently in individuals undergoing periodic physical examination or elective surgery, where a routine blood count reveals the presence of leukemia.

Painless swelling of the easily observed superficial lymph nodes is the most common early symptom of the entire malignant lymphoma group. In some cases, the secondary effect of expansive growth of deep lymph nodes may first call attention to the presence of the disease. Enlargement of mediastinal or bronchial lymph nodes may cause bronchial compression with resultant cough. The development of abdominal masses due to either splenic enlargement or mesenteric adenopathy is relatively frequent. Tumor masses originating in the lymphoid tissues of the stomach or intestine may cause mechanical obstructive symptoms or may produce ulceration of the overlying mucosa with resultant hematemesis or melena.

As a result of involvement of bone marrow, there is usually a decrease in the number of blood platelets so that hemorrhagic signs may appear. Sudden purpuric manifestations unrelated to or disproportionate to trauma are relatively frequent. Severe bleeding following tooth extraction or other minor surgery may occur. Epistaxis or unusual uterine bleeding may be the first indication of disease. Weakness or asthenia are frequent early symptoms which are, in part, related to anemia.

Unexplained fever is a frequent early finding in the malignant lymphomata. Indeed, all of the patient's early symptoms may suggest a low grade infection. Vague aching and pain in the extremities may be one of the subjective symptoms.

The general findings may give all of the clinical indications of the toxemis of tuberculosis. There is frequently unexplained weight loss.

Occasional patients have an initial complaint of generalized pruritis.

* Organized by the Editorial Committee of the California Cancer Commission.

CORRECTION:

Dr. John M. Kenney, whose article, "Childhood Cancer," appeared in this section of the November issue of California Medicine, is practicing in Santa Rosa, California, not in Sonoma as the signature line on the article indicated.

As previously indicated, leukemia of lymphatic type is not differentiated by lymph node morphology. The hematologic observation of leukemia is a variable phenomenon in the group of the malignant lymphomata, being observed most frequently in the lymphocytic lymphoma and lymphoblastic lymphoma groups of the classification of Gall and Mallory, and with equal rarity in their Hodgkin's lymphoma and stem cell lymphoma groups. Leukemia is not regarded, then, as a specific disease entity but rather as one of the objective findings in this general group.

The final classification and diagnosis of this entire group is dependent upon histologic examination.

LYMPHOSARCOMA-LYMPHATIC LEUKEMIA GROUP

Under this broad heading may be included the stem cell, the clasmotocytic, the lymphocytic, the lymphoblastic, and the follicular lymphomas of the morphologic classification. Although these different types show slight individual differences in averages, such as in age incidence, they all exhibit the same general characteristics of the malignant lymphoma.

HODGKIN'S DISEASE

On the basis of the morphologic classification the most commonly encountered lymphoid malignancy is Hodgkin's Disease. As in all of the other malignant lymphoblastomata there is a definite preponderance of males in sex incidence which approximated 3:1.

Commonly a generalized disease involving the superficial and deep lymphoid tissues as a disseminated disease, Hodgkin's is rarely seen as an isolated primary growth originating apparently in the lymphoid tissues of a viscus such as the stomach or small bowel.

More so than the other lymphomas, Hodgkin's Disease is the picture of an infection with febrile manifestation (50%-59%)[1] which occasionally may be accompanied by ague-like chills. The intermittent fever of Pel-Ebstein type occurs with some frequency but is not by any means invariable. Eosinophilia although observed occasionally is not seen frequently in the hematologic picture. Cutaneous lesions are of infrequent occurrence although rarely seen as an initial manifestation. Visceral lesions as mentioned above may be primary. Rare cases of primary pulmonic involvement are seen.

DIFFERENTIAL DIAGNOSIS

Diagnosis of disease of lymphoid tissue must consider inflammatory processes, as well as malignancy. The grave portent of the diagnosis of lymphatic malignancy should demand that consideration of all other possibilities be exhausted before final classification is made.

The lymphatic tissues, as a series of filters in the lymphatic channels which transport particulate matter and substances in solution, respond readily to injury with inflammation and hyperplasia. The common result of such response is lymph node enlargement.

It is possible for any of the inflammatory lesions of lymphoid tissue to simulate malignancy both in clinical manifestation and microscopic appearance. Syphilis can be overlooked and misdiagnosed as malignancy. Other inflammatory lesions have been, and undoubtedly will be, similarly misinterpreted. The following outline is meant to illustrate in a general way the various inflammatory lymphadenopathies which may masquerade as malignancies and which, therefore, should be considered:

CAUSES OF INFLAMMATORY LYMPHADENOPATHY

A. Local acute lymphadenitis:
   1. Acute focal pyogenic infections.
   2. Primary specific infections.
      (a) Syphilis ("cryptic" chancre).
      (b) Other infectious granulomas.
      (c) Acute lesions of lymphogranuloma venereum.
      (d) Tularemia with occult primary lesion.
      (e) Bubonic plague (endemic in California).

B. Local chronic lymphadenitis:
   1. Chronic pyogenic infection.
   2. Chronic specific infections.

C. Acute generalized lymphadenitis:
   1. Infectious mononucleosis.
   2. Infectious lymphocytosis.
   3. Leukemoid reaction.
   4. Exanthematous infections.
   5. Infectious granulomata.

D. Chronic generalized lymphadenitis:
   1. Infectious granulomata.
   2. Tularemia.
   3. Undulant fever.
   4. Glanders.

As the outline indicates, the infectious granulomata may be the cause of lymphadenopathy, whether local, generalized, acute, or chronic. Some of the more obscure infections, such as glanders (b. mallei), tularemia, and undulant fever, are more likely to be overlooked because of their infrequent incidence.

Infectious mononucleosis, even today, is mistaken for leukemia or other of the malignant lymphomas. The heterophile antibody test is not infallible in diagnosis. There are certain cases which do not ever demonstrate the heterophile phenomenon. Early in the disease, the test is frequently negative. Diagnosis requires competent hematologic examination.

Infectious lymphocytosis, undoubtedly has been mistaken for lymphatic leukemia as have pertussis, infectious parotitis, measles, and other of the acute infections of childhood which produce lymphatic reaction.

Leukemoid reaction is seen occasionally, particularly in childhood, when the lymphoid tissues are more active and labile. These tissues frequently respond to injury with dissemination of immature, toxic appearing leukocytes into the peripheral blood. This type of reaction is undoubtedly the entire source of the "recovered" cases of leukemia.

In patients showing lymphadenopathy, whether generalized or regional, where the process cannot be attributed to inflammation, the possibility of malignant lymphoblastoma should be borne in mind and the use of lymph node biopsy considered, particularly in those cases where apparent inflammatory

association is demonstrated but where the nodes fail to regress.

In any case with hemorrhagic manifestations, examination of the blood for evidence of malignant lymphoblastoma is warranted.

With involvement of the deeply situated mediastinal or abdominal lymph nodes, there may be evidence of the systemic effects of the malignancy without externally demonstrable tumor. Lesions of this character are difficult to demonstrate by any other means than x-ray.

Lymphadenopathy, particularly in the cervical region, may be the result of "silent" primary carcinomas of oral and nasopharyngeal origin. Less frequently carcinoma in other situations may give rise to distant or widespread involvement of lymphoid tissues.

BIOPSY

Diagnosis in the great majority of the cases of this group is dependent upon biopsy.

In the performance of biopsy one cannot overemphasize the importance of certain technical considerations which are briefly enumerated:

1. *Selection of area for biopsy:*

If there is a choice of biopsy site, lymph nodes from the inguinal area should be avoided. These nodes commonly show chronic inflammatory changes which frequently are of such severity that they are not suitable for diagnosis.

2. *Selection of individual lymph nodes:*

It is preferable to select the largest, or one of the largest, lymph nodes, rather than one which is only slightly enlarged. This statement is made on the basis of the fact that the larger lymph node will offer a more representative picture of the disease process. The small node may not even be involved.

3. *Avoidance of trauma to biopsy tissue:*

The biopsy is performed to obtain information by microscopic examination. Therefore, all consideration should be directed to the care of the biopsy specimen. In process of removal it should not be compressed by clamps or forceps. Compression of even slight degree causes traumatic artifacts of the extremely delicate lymphoid tissues so that they may be rendered unfit for examination. After removal, the specimen should not be palpated, incised, squeezed, or massaged, but given to the pathologist at once.

4. *Care of tissues when the biopsy is to be mailed:*

When the tissue is to be mailed to a pathologist and will be any time in transit, it is wise in order to insure fixation, to incise the tissue with a sharp knife in its midline long axis and from one of the pieces cut a slice of tissue measuring no more than 4 mm. in thickness. The tissues should then be placed immediately in a volume of fixative at least 10 times that of the tissue. Choice of fixatives varies as do pathologists. For general purposes, readily available 10 per cent formalin is satisfactory.

5. The pathologist should always be supplied with complete blood count and Wassermann reports and a blood smear should be sent with the biopsy specimen.

TREATMENT

Roentgen radiation is the only form of therapy which has proved to be effective in any significant degree as demonstrated over a period of years on large numbers of cases. The malignant lymphomata as a group react favorably and rapidly to relatively small amounts of radiation. It is occasionally observed that radiation of a single group of lymph nodes involved in a lymphomatous process will result in coincident reduction in size of involved lymph nodes in other body areas. The beneficial effects of Roentgen radiation are effective in palliation, prolongation of life, and in relief of obstruction, but are not curative. Tumors may reappear in treated areas immediately after completion of a course of therapy. Initial resistance to radiation therapy was encountered in 9 per cent of all of the cases studied by Gall and Mallory. Terminally, in some cases there is a marked resistance to irradiation.

Radio-active phosphorus has been used extensively in the treatment of malignant lymphomas. The results have been disappointing. In general, it has proven to be less effective than x-ray therapy.[3] The material has been used experimentally and is not available for general distribution.

Nitrogen mustard therapy (the use of hyoginated akyl amines), has been the subject of recent studies and the reports are somewhat favorable. These reports indicate that some cases resistant to radiation respond favorably to nitrogen mustards and that following such therapy responsiveness to radiation may be increased. Goodman, et al.,[2] make the following comment in discussion of their recently published results: "Although indications and contraindications for the use of nitrogen mustards remain to be established definitely, it is felt that these agents are deserving of further clinical trial in Hodgkin's Disease, lymphosarcoma, and leukemia. Like radiation, they do not cure."

SURGERY

The accepted concept of the malignant lymphomatous diseases is that they are the expression of a generalized disseminated process. There are, however, well authenticated, histologically verified cases where removal, or intensive irradiation, of a solitary localized visceral or skeletal lesion has been curative. Although the number of these cases is small, the definite character of the lesion and the possibility of favorable result should justify consideration of surgery where there is a demonstrated solitary lesion. Lesions of the tonsil and gastro-intestinal tract are the ones most likely to be cured by radical treatment.

PROGNOSIS

Prognosis in the average case in this disease group is most doleful. It is possible, on the basis of histologic classification of the lesion, to determine prog-

nosis in a general way insofar as survival period is concerned. The less differentiated lymphoblastic lymphomas, the stem cell lymphomas, and the clasmotocytic lymphomas show a very small percentage of cases with five-year survival. The more differentiated follicular lymphoma and lymphocytic lymphoma show approximately 50 per cent of the total number which survive for five years after diagnosis. Hodgkin's sarcoma which represents only a small percentage of the total is a much more malignant form of the disease than Hodgkin's lymphoma which shows five-years survivals in roughly one-third of the cases.

REFERENCES

1. Gall, E. A. and Mallory, T. B.: Malignant lymphoma; clinico-pathologic survey of 618 cases, American Journal of Pathology, 18:381 (May), 1942.

2. Goodman, L. S., Wintrobe, M. M., Gilmon, A. and McKennon, M. T.: J.A.M.A., 132:126, 1946.

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"Cancer of the Lip" by Ian Macdonald, M.D., Chapter XI of the California Cancer Commission Studies will appear in this section of the January issue of CALIFORNIA MEDICINE. *Chapters IX and X on "Cancer of the Skin" will be published later.*